# Suppression of nocturnal fatty acid concentrations by bedtime carbohydrate supplement in type 2 diabetes: effects on insulin sensitivity, lipids, and glycemic control[1–3]

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**ABSTRACT**

**Background**: Bedtime ingestion of slow-release carbohydrates leads to sustained nocturnal fatty acid suppression and improved glucose tolerance in type 2 diabetic patients.

**Objective**: This study assessed the effects of 2 different doses of bedtime carbohydrate supplement (BCS) on morning glycemic control and glycated hemoglobin (Hb $A_{1c}$) in type 2 diabetic patients. In addition, the effects of the high-dose BCS on insulin sensitivity and postprandial glucose and triacylglycerol concentrations were assessed.

**Design**: Two BCS doses were studied separately in 7-wk randomized, placebo-controlled, double-blind studies with either a parallel (low-dose BCS; $n = 24$ patients) or crossover (high-dose BCS; $n = 14$ patients) design. The effects of the low and high doses (0.30 and 0.55 g uncooked cornstarch/kg body wt, respectively) were compared with those of a starch-free placebo.

**Results**: Compared with the starch-free placebo, the high-dose BCS (≈45 g) produced enhanced nocturnal glucose ($P < 0.01$) and insulin ($P < 0.01$) concentrations as well as a 32% suppression of fatty acid concentrations ($P < 0.01$). Moreover, glucose tolerance ($P < 0.05$) and C-peptide response ($P < 0.05$) improved after breakfast the next morning. The low-dose BCS (≈25 g) improved fasting blood glucose concentrations ($P < 0.05$). However, there were no improvements in insulin sensitivity, postprandial triacylglycerol concentrations, or Hb $A_{1c}$ after 7 wk.

**Conclusion**: Nocturnal fatty acid suppression by BCS improved fasting and postprandial blood glucose concentrations in type 2 diabetic patients the next morning. In contrast, no improvements in insulin sensitivity, postprandial triacylglycerol concentrations, or long-term glycemic control assessed by Hb $A_{1c}$ were seen after BCS supplementation. *Am J Clin Nutr* 2000;71:1108–14.

**KEY WORDS** Type 2 diabetes mellitus, fatty acids, glucose, C-peptide, triacylglycerol, insulin sensitivity, diurnal changes

## INTRODUCTION

Type 2 diabetic patients experience important diurnal changes in insulin sensitivity, with insulin resistance being more pronounced in the morning than in the afternoon (1–3). This, combined with a decreased β cell response (2), leads to elevated systemic glucose production in the morning (3). Insulin exerts a signaling effect to suppress the systemic glucose output, and this effect appears to be exerted mainly through the suppression of plasma fatty acid concentrations (4–6). Fatty acids (7, 8) and insulin (9) also play an important role in hepatic lipoprotein secretion. Hence, both triacylglycerol and glucose concentrations seem to be closely linked to plasma fatty acid concentrations. Because nocturnal concentrations of plasma fatty acids are elevated in type 2 diabetic individuals (10), control of nocturnal lipolysis may improve both glucose and triacylglycerol metabolism in type 2 diabetes, as also supported by short-term experiments with the nicotinic acid analog acipimox (11–13).

Uncooked cornstarch, a source of slowly releasable dietary carbohydrates as measured in vivo (14) and in vitro (15), elicits a low blood glucose peak, yet it produces an elevated blood glucose concentration for ≈7 h in patients with glycogen storage disease (16–18) and type 1 diabetes (19). We showed that ingestion of a bedtime carbohydrate supplement (BCS; 100 g uncooked cornstarch) for 2 d was associated with a marked and sustained suppression of nocturnal fatty acid concentrations in type 2 diabetic patients (20). We also showed, for the first time, improved glucose tolerance after breakfast on the morning subsequent to bedtime ingestion of uncooked starch, which is consistent with an overnight second-meal effect in type 2 diabetes (20). However, we also observed that the large dose of BCS resulted in excessive nocturnal blood glucose concentrations in these patients. The effects of nocturnal fatty acid suppression on postprandial triacylglycerol concentrations were not assessed.

In the present study, we examined the effects of an individually titrated BCS dose on insulin sensitivity, postprandial triacylglycerol concentrations, and glycemic control in type 2

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**TABLE 1**
Characteristics of the study groups at baseline[1]

| | High-dose study (0.55 g/kg body wt) ($n$ = 11 M, 3 F) | Low-dose study[2] (0.30 g/kg body wt) | |
|---|---|---|---|
| | | BCS ($n$ = 7 M, 5 F) | Placebo ($n$ = 7 M, 5 F) |
| Age (y) | 56 ± 7[3] | 61 ± 9 | 60 ± 13 |
| Weight (kg) | 88.3 ± 12.1 | 86.5 ± 15.0 | 86.0 ± 12.8 |
| Body mass index (kg/m$^2$) | 29.2 ± 2.8 | 28.8 ± 2.7 | 28.8 ± 5.3 |
| Waist-hip ratio | 0.96 ± 0.05 | 0.94 ± 0.07 | 0.96 ± 0.08 |
| Fasting blood glucose (mmol/L) | 8.4 ± 1.7 | 7.6 ± 1.6 | 7.2 ± 1.3 |
| Fasting insulin | | | |
| (pmol/L) | 87.6 ± 35.4 | 67.2 ± 8.4 | 89.4 ± 10.8 |
| (mU/L) | 14.6 ± 5.9 | 11.2 ± 1.4 | 14.9 ± 1.8 |
| Hb $A_{1c}$ | 0.068 ± 0.010 | 0.061 ± 0.009 | 0.062 ± 0.009 |
| Diabetes treatment ($n$) | | | |
| Diet alone | 3 | 10 | 8 |
| Sulfonylurea | 7 | 0 | 0 |
| Metformin | 4 | 2 | 4 |

[1] BCS, bedtime carbohydrate supplement; Hb $A_{1c}$, glycated hemoglobin.
[2] There were no significant differences at baseline between groups.
[3] $\bar{x}$ ± SD.

diabetic patients. Because this dose was a larger bedtime snack than that normally consumed by these patients, we also studied the effects of a smaller dose on fasting blood glucose control and glycated hemoglobin (Hb $A_{1c}$).

## SUBJECTS AND METHODS

### Subjects

Patients with type 2 diabetes were recruited by advertisement in a local newspaper and gave informed consent to the protocol, which was approved by the Ethical Committee of Göteborg University. At entry to the study (baseline), diabetes therapy consisted of diet alone or diet combined with oral medication, which remained unchanged during the study. None of the patients were receiving combination therapy (ie, multiple oral diabetes medications). Swedish dietary guidelines prescribe 55% of energy from carbohydrates, 30% from fat, and 15% from protein. The patients were asked to not modify their regular diet or exercise habits during the study.

### High-dose study

In 14 patients with type 2 diabetes, the effects of a high dose of BCS (0.55 g uncooked cornstarch/kg body wt) were studied in a randomized, placebo-controlled, double-blind, crossover fashion. The exclusion criteria were *1*) fasting blood glucose >12.0 mmol/L, *2*) glycated Hb $A_{1c}$ >0.10 (reference range: 0.033–0.053) and, *3*) treatment with insulin. Characteristics of the patients at baseline, including the type of treatment they were receiving, are shown in **Table 1**.

The study lasted from September to April. There were 2 periods, each of which lasted 7 wk and was separated by an 11-wk washout period (from December to February). The BCS and placebo were consumed at 2200, were premixed and provided in jars, and had identical appearances; the granular texture of raw cornstarch was well masked. For active treatment, the patients received daily 0.55 g BCS (uncooked cornstarch)/kg body wt providing 8.4 J/kg (CPC Foods AB, Kristianstad, Sweden) dissolved in low-sugar fruit juice (1.7 J/kg body wt). The placebo contained an equal amount of low-sugar fruit juice as well as white food-coloring and thickening agents (citrus pectin, 0.033 g/kg body wt). The placebo and BCS provided 0.59 and 0.10 g carbohydrate/kg body wt, respectively, according to national food tables.

Metabolic investigations were conducted at baseline and after each supplement period. The patients adhered to an individually standardized menu and abstained from alcohol and physical activity for 24 h preceding each investigation. Changes in Hb $A_{1c}$ and body weight after 7 wk were recorded.

Insulin sensitivity was assessed by the euglycemic hyperinsulinemic clamp technique, as described previously (21), with an insulin infusion rate of 1.0 mU · kg$^{-1}$ · min$^{-1}$ and a clamped glucose concentration of 6 mmol/L for a total of 120 min. The average glucose infusion rate during the final 30 min of steady state was used to estimate the glucose infusion rate. Lean body mass was calculated from total-body $^{40}$K determined in a whole-body counter (22). Insulin sensitivity is expressed as glucose infusion rate/lean body mass (mg · min$^{-1}$ · kg$^{-1}$).

The investigations also included an overnight study and a glucose tolerance test after breakfast on the following morning. Arterialized blood samples were collected from a heated forearm at −10 and 0 min (2200). The BCS and placebo supplement were consumed at 2205. Blood samples were drawn every 0.5 h for 2 h (2200–2400), every 2 h for 6 h (0000–0600), and then every 0.5 h for 7 h (0600–1300). In the morning, the patients took their regular diabetes medication at 0630 and a fat-rich breakfast was served at 0700. The breakfast was designed to produce a clear rise in serum triacylglycerol and consisted of a sandwich of white bread with margarine, lettuce, tomatoes, cheese, and ham and a cup of hot chocolate with cream. The breakfast provided 3.86 MJ, of which 33 g (14%) was from protein, 51 g (49%) was from fat, and 83 g (36%) was from carbohydrate (23). The amount of saturated, monounsaturated, and polyunsaturated fat in the meal was 30, 15, and 3 g, respectively; the ratio of polyunsaturated to saturated fat was 0.1. The postprandial blood glucose concentration was

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assessed every 30 min and insulin, fatty acid, lactate, and lipid concentrations were assessed every hour for 6 h. C-peptide concentrations were measured before and 1 and 2 h after the meal.

### Low-dose study

In another group of 24 patients with type 2 diabetes, the effects of a low dose of BCS (0.30 g uncooked cornstarch/kg body wt) were studied in a randomized, placebo-controlled, double-blind, parallel fashion with 12 patients in each group. Each patient was individually matched with another patient for sex, fasting blood glucose concentration, Hb $A_{1c}$, and body mass index (in $kg/m^2$). Because the ability of the pancreas to release insulin is critical for achieving improved glycemic control, the effects of the low-dose BCS were studied in patients with well-controlled diabetes who did not require treatment with sulfonylurea. Hence, the exclusion criteria were *1*) fasting blood glucose >10.0 mmol/L, *2*) Hb $A_{1c}$ >0.08, and *3*) treatment with insulin or sulfonylurea. Two patients in each group were treated with β-blocking agents. Characteristics of the patients at baseline, including the type of treatment they were receiving, are shown in Table 1.

Each pair of patients was randomly stratified to receive either the placebo or BCS. One patient was entered into the study within a week of the other to exclude seasonal effects on blood glucose control. The design was similar to that of the high-dose study. Treatment periods lasted 7 wk and the supplements were consumed at ≈2200. The placebo and BCS were prepared in a fashion similar to that for the high-dose study. However, the BCS dose was less, 0.30 g uncooked cornstarch/kg body wt (4.2 J/kg body wt), as were the doses of low-sugar fruit juice (0.9 J/kg body wt) and pectin (0.018 g/kg body wt). The BCS and placebo provided 0.33 and 0.06 g carbohydrate/kg body wt, respectively.

The patients, who had fasted since 2200 the previous evening, came to the laboratory at 0800 for venous blood sampling. Treatment effects were assessed as the change in fasting blood glucose, insulin, lactate, fatty acids, and Hb $A_{1c}$ after 4 and 7 wk. Change in body weight was assessed after 7 wk. Nocturnal metabolic control, insulin sensitivity, and glucose tolerance after breakfast were not investigated in this part of the study.

### Blood chemistry

Hb $A_{1c}$ was analyzed by using an automated HPLC method. Blood glucose and lactate were measured with an automatic glucose analyzer (Yellow Springs Instruments, Yellow Springs, OH). Plasma insulin was determined by radioimmunochemical analysis (Pharmacia Insulin RIA; Pharmacia AB, Uppsala, Sweden). C-peptide concentrations (reference range: 1.1–1.7 μg/L) were determined with immunoenzymometric analysis (Dako Diagnostics Ltd, Cambridgeshire, United Kingdom). Plasma fatty acid concentrations were determined with an enzymatic colorimetric method (Wako Chemicals GmbH, Neuss, Germany). Serum triacylglycerol and cholesterol were determined with an automated Cobas Mira analyzer (Hoffmann-La Roche, Basel, Switzerland) with enzymatic methods. The concentration of HDL cholesterol was measured by the phosphotungstic acid–magnesium chloride precipitation method.

## STATISTICAL ANALYSES

Data are presented as means ± SEs unless otherwise stated. The incremental area under the curve (IAUC) above baseline or the area under the curve (AUC) above zero were calculated according to the trapezium rule (24). Treatment effects were calculated as the individual differences between the responses to the BCS and placebo supplement (ie, ΔBCS − Δplacebo); statistical significance was evaluated with the nonparametric one-sample sign test (25). Significant differences between baseline and postsupplement values and unpaired comparisons between subgroups in the high-dose study were calculated with Wilcoxon's paired rank-sum test and the Mann-Whitney *U* test, respectively. In the low-dose study, significant differences between baseline and postsupplement values between matched pairs were calculated with Wilcoxon's paired rank-sum test. A factorial analysis of the effect of supplement order on Hb $A_{1c}$ was performed with one-way analysis of variance within groups. Linear relations were determined by simple and multiple regression analyses. All tests were two-tailed and a $P$ value <0.05 was considered statistically significant.

## RESULTS

Compliance, assessed by counting leftover supplement jars and interviewing the subjects, was ≥90%. No gastrointestinal side effects were reported.

### High-dose study

There was no significant change in body weight (0.4 ± 0.3 kg) during the 7 wk of treatment. After the study, only 2 subjects correctly estimated the treatment order, whereas one subject made a false estimation. All other subjects reported that they could not distinguish between the supplements. Hb $A_{1c}$ values tended to be elevated after the washout period compared with baseline, but this effect was independent of treatment order ($P = 0.83$).

#### *Nocturnal and postprandial metabolic variables*

Consumption of the BCS was associated with an increase in the blood glucose concentration of 2.1 ± 0.4 mmol/L between 0200 and 0700 ($P < 0.01$; **Figure 1**). While the early morning glucose concentration was continuously decreasing until 0700 after the BCS, there was a significant rise from the nocturnal nadir to 0700 ["dawn phenomenon" (1)] both at baseline (0.7 ± 0.2 mmol/L; $P < 0.001$) and after the placebo (0.8 ± 0.2 mmol/L; $P < 0.001$). The insulin concentration increased by 30.6 ± 9.6 pmol/L (5.1 ± 1.6 mU/L) between 0200 and 0700 after the BCS ($P < 0.01$) and was associated with a 32% suppression of nocturnal fatty acid concentrations ($P < 0.01$; Figure 1). The observed increased nocturnal glucose metabolism after the BCS supplement was mirrored by 20% higher lactate concentrations ($P < 0.01$).

The fasting fatty acid concentration remained significantly suppressed (by 30%) after the BCS ($P < 0.05$; Figure 1). Fasting blood glucose and plasma insulin concentrations were not significantly different. Despite a tendency for the fasting blood glucose concentration to increase after the high-dose BCS, the 6-h postprandial IAUC for glucose was 36% lower ($P < 0.05$; Figure 1). Insulin secretion, measured as postprandial C-peptide concentrations, increased by 40% after the BCS ($P < 0.05$; **Table 2**). However, fasting and postprandial triacylglycerol concentrations, expressed as the IAUC or AUC, were not significantly affected by the BCS (**Figure 2**). Fasting and postprandial concentrations of total cholesterol, HDL-cholesterol, apolipoprotein (apo) B, and apo A concentrations were not significantly different from placebo (data not shown).

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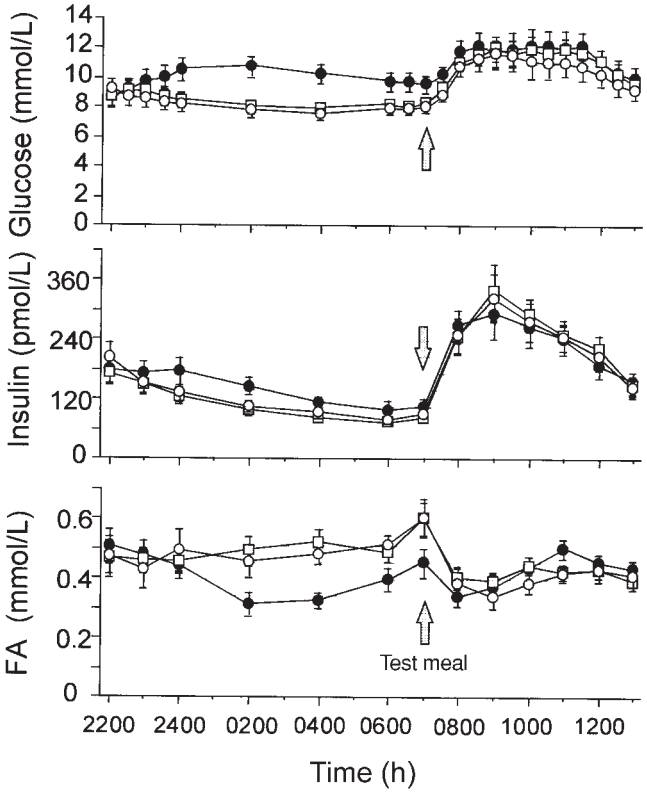


**FIGURE 1.** Mean (±SE) nocturnal and morning postprandial glucose, insulin, and fatty acid (FA) concentrations at baseline (○) and after ingestion at 2200 of a starch-free placebo (□) or a high dose of bedtime carbohydrate supplement (0.55 g uncooked cornstarch/kg body wt) (●). There was a significant treatment effect on the area under the curve for glucose, insulin, and FAs (0200–0700) and for the incremental area under the curve for glucose (0700–1300).

*Long-term glycemic control*

There were no significant changes in Hb $A_{1c}$ values after 7 wk of the BCS. Hb $A_{1c}$ decreased by 0.002–0.007 (0.004 ± 0.001) in 6 subjects, increased by 0.001–0.013 (0.005 ± 0.002) in 7 subjects, and did not change in 1 subject. Multiple regression analysis showed that the changes in nocturnal insulin and fasting blood glucose concentrations were independent determinants of the effect of BCS on Hb $A_{1c}$ (**Table 3**). Individual changes in fasting triacylglycerol were, in turn, positively and linearly related to the change in Hb $A_{1c}$ ($r = 0.57$, $P < 0.05$).

*Insulin sensitivity*

There were no significant differences in glucose, insulin, fatty acid, or lactate concentrations at baseline or at steady state conditions during the euglycemic clamp (data not shown) between groups. There was no significant effect of BCS on insulin sensitivity ($-0.2 \pm 0.2$ mg · $min^{-1}$ · $kg^{-1}$).

**Low-dose study**

The change in body weight after 7 wk did not differ significantly (0.0 ± 0.5 compared with 0.8 ± 0.3 kg in the BCS and placebo periods, respectively). In this study, 5 patients correctly estimated whether they had received the BCS or placebo treatment, whereas 3 patients made a false estimate.

*Fasting metabolic variables*

Fasting metabolic variables at baseline and changes after 4 and 7 wk of BCS or placebo treatment are shown in **Table 4**. The low-dose BCS was associated with significantly lower fasting blood glucose concentrations compared with the placebo supplement after both 4 and 7 wk by an average of 0.8 ± 0.4 ($P < 0.05$) and 0.9 ± 0.4 ($P < 0.05$) mmol/L, respectively. Other fasting metabolic variables were not significantly different.

*Long-term glycemic control*

Hb $A_{1c}$ values were stable and not significantly different in the 2 supplement periods (Table 4). Hb $A_{1c}$ values were significantly lower by 0.002–0.01 ($\bar{x}$: 0.005) after the BCS than after the placebo in 6 of the subject pairs, significantly higher by 0.001–0.006 ($\bar{x}$: 0.004) in 5 of the subject pairs, and not significantly different in 1 of the subject pairs.

## DISCUSSION

We reported previously that a high dose of uncooked cornstarch (100 g) ingested at bedtime for 2 d increased nocturnal glucose and insulin concentrations and decreased plasma fatty acid concentrations (20). These effects were associated with improved blood glucose tolerance after a standardized breakfast, a so-called second-meal effect. The pivotal role of the slow-release profile of the uncooked cornstarch in eliciting this effect is supported by the finding that the same effect is not obtained with similar amounts of white bread (15). These initial findings were extended by the present study, in which 2 smaller doses of BCS were used to produce minor elevations in nocturnal blood glucose concentrations. It is clear that the higher BCS dose (0.55 g/kg body wt) ingested at 2200 was sufficient to reduce nocturnal fatty acid concentrations and maintain this

**TABLE 2**
Fasting and postprandial C-peptide concentrations before and after ingestion of a high dose of bedtime carbohydrate supplement (BCS) or placebo for 7 wk in type 2 diabetic patients[1]

| C-peptide | Baseline | After BCS | After placebo | Treatment effect[2] |
|---|---|---|---|---|
| | | *μg/L* | | |
| Fasting | 1.0 ± 0.1 | 0.9 ± 0.2 | 0.7 ± 0.1 | 0.2 ± 0.2 |
| Δ60 min | 0.6 ± 0.2 | 1.0 ± 0.2 | 0.9 ± 0.2 | 0.2 ± 0.2 |
| Δ120 min | 1.0 ± 0.2 | 1.3 ± 0.3 | 0.9 ± 0.3 | 0.4 ± 0.2[3] |

[1] $\bar{x}$ ± SE; $n = 10$. The high-dose BCS was 0.55 g uncooked cornstarch/kg body wt.
[2] ΔBCS − Δplacebo.
[3] $P = 0.0215$

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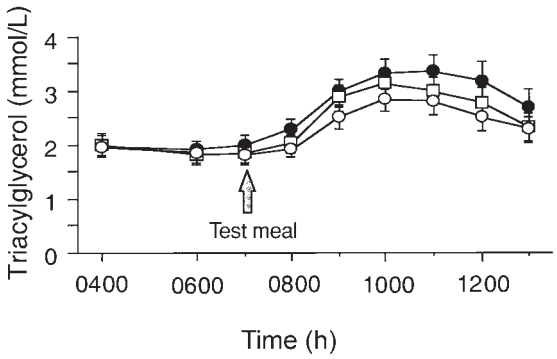


**FIGURE 2.** Mean (±SE) morning postprandial triacylglycerol concentrations at baseline (○) and after ingestion at 2200 of a starch-free placebo (□) or a high dose of bedtime carbohydrate supplement (0.55 g uncooked cornstarch/kg body wt) (●). There were no significant treatment effects.

reduction (≈30%) to 0700, a common breakfast time. Moreover, we also showed for the first time a favorable effect of the low BCS dose (0.30 g/kg body wt) on fasting blood glucose concentrations in patients with mild type 2 diabetes. Hence, the overnight second-meal effect may only require modest amounts (<25 g) of slow-release carbohydrates at bedtime in patients with mild type 2 diabetes.

Several factors influence triacylglycerol concentrations in the postabsorptive and postprandial states. Fatty acids, for instance, are the main substrate for VLDL-triacylglycerol synthesis (7, 26) and they stimulate apo B secretion from the liver (8). The reduction in fatty acid concentrations by the antilipolytic agent acipimox (12, 27) and the reduction in fatty acid oxidation by the antilipolytic agent etomoxir (28) lead to improved triacylglycerol concentrations in type 2 diabetic patients. Insulin, in contrast, inhibits hepatic VLDL output and apo B production (9, 29, 30) during hyperinsulinemic euglycemic clamp conditions, even if this effect is decreased in type 2 diabetes (8, 9, 31). Moreover, improved insulin sensitivity by, for instance, metformin improves postprandial triacylglycerol concentrations (32). In contrast, carbohydrate-induced hyperinsulinemia in type 2 diabetes leads to an accentuated postprandial output of VLDL triacylglycerol (33, 34). In the present study, the balanced effect of carbohydrate-induced hyperinsulinemia on fasting and postprandial triacylglycerol concentrations, when combined with a marked decrease in nocturnal fatty acid concentrations, was indistinguishable from the placebo effect. This may have been due to the choice of a fat-rich breakfast, which predominantly reflects chylomicron concentrations. Alternatively, the fact that insulin resistance was not alleviated by the slow-release BCS might explain why the BCS had no significant effect on postprandial triacylglycerol concentrations.

In line with our previous findings (15, 20), glucose tolerance after breakfast, measured as the absolute increase in glucose concentrations, improved after the BCS (by 36%), consistent with an overnight second-meal effect (35). However, this effect was obscured by the fact that there was a nonsignificant tendency for higher fasting glucose concentrations after the high-dose BCS (Figure 1).

It is clear from the present results that the second-meal effect after BCS ingestion was not due to alleviation of peripheral insulin resistance. Possible mechanisms for the improved glucose tolerance include improved pancreatic insulin release and decreased hepatic glucose output. Elevated fatty acid concentrations can exert a lipotoxic effect on pancreatic insulin release (36, 37). The fact that BCS ingestion enhanced postprandial C-peptide concentrations supports the possibility of improved pancreatic insulin release (Table 2). Thus, an increased release of insulin after breakfast may, at least in part, explain the overnight second-meal effect. Unfortunately, glucose output was not assessed with the clamp protocol.

Long-term glycemic control, determined on the basis of Hb $A_{1c}$ values, did not improve after 7 wk of BCS ingestion. This finding suggests that the second-meal effect of BCS was too short or too small to compensate for the excess carbohydrate intake. However, because diabetic patients have impaired pancreatic insulin secretion, it can be speculated that BCS may be more appropriate in obese people with impaired glucose tolerance who frequently have normal or high insulin concentrations and high fatty acid concentrations (38, 39).

The finding that the nocturnal serum insulin concentration was an independent determinant of Hb $A_{1c}$ values is a new observation, suggesting that nocturnal insulinopenia, rather than hyperinsulinemia, is responsible for poor glycemic control (Table 3). Furthermore, recent evidence clearly indicates that the inhibitory effect of insulin on glucose production is indirect and mediated through a reduction in fatty acid concentrations (4, 6). Whether BCS would prevent or delay the development of manifest diabetes by enhanced insulin concentrations and lowered fatty acid concentrations in subjects with impaired glucose tolerance is, thus, an intriguing possibility worthy of study.

In summary, BCS ingestion by type 2 diabetic patients increased nocturnal insulin and reduced fatty acid concentrations. These effects were associated with improved fasting blood glucose concentrations and improved glucose tolerance and C-peptide responses after a fat-rich breakfast the next morning. However, postprandial triacylglycerol concentrations were not improved, possibly because insulin resistance was not

**TABLE 3**
Multiple regression analysis of relations between metabolic variables and glycated hemoglobin (Hb $A_{1c}$)[1]

| Dependent variable | Independent variables | *P* | Standardized $r^2$ | Model $r^3$ |
|---|---|---|---|---|
| Hb $A_{1c}$ | Nocturnal insulin AUC | 0.005 | −0.579 | 0.87 |
| Hb $A_{1c}$ | Fasting blood glucose | 0.042 | 0.439 | — |
| Hb $A_{1c}$ | Nocturnal FA AUC | 0.100 | 0.339 | — |

[1] AUC, area under curve; FA, fatty acids.
[2] For each of the individual independent variables.
[3] For the independent variables combined.

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**TABLE 4**
Fasting metabolic variables before and after ingestion of a low dose of bedtime carbohydrate supplement (BCS) or placebo for 7 wk in type 2 diabetic patients[1]

| | Baseline | | Change at 4 wk[2] | | Change at 7 wk | |
|---|---|---|---|---|---|---|
| | BCS | Placebo | BCS | Placebo | BCS | Placebo |
| Blood glucose (mmol/L) | 7.7 ± 0.5 | 7.2 ± 0.4 | 0.6 ± 0.2[3] | 1.4 ± 0.4 | 0.0 ± 0.4[3] | 1.0 ± 0.3 |
| Hb $A_{1c}$ | 0.061 ± 0.003 | 0.062 ± 0.003 | 0.0 ± 0.001 | 0.0 ± 0.001 | −0.001 ± 0.001 | 0.0 ± 0.001 |
| Insulin | | | | | | |
| (pmol/L) | 67.2 ± 8.4 | 89.4 ± 10.8 | 4.2 ± 2.4 | −1.2 ± 9.6 | −0.6 ± 4.8 | 11.4 ± 7.8 |
| (mU/L) | 11.2 ± 1.4 | 14.9 ± 1.8 | 0.7 ± 0.4 | −0.2 ± 1.6 | –0.1 ± 0.8 | 1.9 ± 1.3 |
| C-peptide (μg/L) | 1.9 ± 0.1 | 2.3 ± 0.2 | 0.2 ± 0.1 | 0.1 ± 0.1 | 0.2 ± 0.1 | 0.2 ± 0.1 |
| Fatty acids (mmol/L) | 0.61 ± 0.11 | 0.60 ± 0.06 | 0.00 ± 0.07 | 0.19 ± 0.11 | −0.03 ± 0.10 | 0.01 ± 0.09 |
| Lactate (mmol/L) | 1.09 ± 0.10 | 1.34 ± 0.08 | 0.26 ± 0.07 | 0.20 ± 0.14 | 0.06 ± 0.07 | 0.06 ± 0.10 |

[1] $\bar{x}$ ± SE; $n$ = 24. The low dose of BCS was 0.30 g uncooked cornstarch/kg body wt.
[2] $n$ = 22.
[3] Significantly different from placebo, $P < 0.05$.

alleviated by BCS ingestion. Further studies are warranted to test the effects of BCS ingestion in patients with impaired glucose tolerance and to see whether the progression of the disease can be delayed.

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## REFERENCES


1. Bolli G. The dawn phenomenon: its origin and contribution to early morning hyperglycemia in diabetes mellitus. Diabetes Metab 1988; 14:675–86.
2. Shapiro E, Polonsky K, Copinschi G, et al. Nocturnal elevation of glucose levels during fasting in noninsulin-dependent diabetes. J Clin Endocrinol Metab 1991;72:444–54.
3. Perriello G, Pimenta W, Pampanelli S, et al. Evidence of day-night changes in insulin sensitivity in type 2 diabetes mellitus. Diabetologia 1998;41(suppl):A194 (abstr).
4. Rebrin K, Steil G, Getty L, Bergman R. Free fatty acid as a link in the regulation of hepatic glucose output by peripheral insulin. Diabetes 1995;44:1038–45.
5. Rebrin K, Steil G, Mittelman S, Bergman R. Causal linkage between insulin suppression of lipolysis and suppression of liver glucose output in dogs. J Clin Invest 1996;98:741–9.
6. Mittelman S, Fu Y, Rebrin K, Steil G, Bergman R. Indirect effect of insulin to suppress endogenous glucose production is dominant, even with hyperglucagonemia. J Clin Invest 1997;100:3121–30.
7. Havel R, Kane J, Balasse O, Segel N, Basso L. Splanchnic metabolism of free fatty acids and the production of triglycerides of very low density lipoproteins in normotriglyceridemic and hypertriglyceridemic humans. J Clin Invest 1970;49:2017–35.
8. Byrne C, Wang T, Hales C. Control of Hep G2-cell triacylglycerol and apolipoprotein B synthesis and secretion by polyunsaturated non-esterified fatty acids and insulin. Biochem J 1992;288:101–7.
9. Lewis G, Uffelman K, Szeto L, Steiner G. Effects of acute hyperinsulinemia on VLDL triglyceride and VLDL apoB production in normal weight and obese individuals. Diabetes 1993;42:833–42.
10. Reaven G, Hollenbeck C, Jeng C-Y, Wu M, Chen Y. Measurement of plasma glucose, free fatty acid, lactate and insulin for 24 h in patients with NIDDM. Diabetes 1988;37:1020–4.
11. Vaag A, Skött P, Damsbo P, Gall M, Richter E, Beck-Nielsen H. Effect of the antilipolytic nicotinic acid analogue acipimox on whole-body and skeletal muscle glucose metabolism in patients with non-insulin-dependent diabetes mellitus. J Clin Invest 1991;88:1282–90.
12. Saloranta C, Groop L, Ekstrand A, Franssila-Kallunki A, Eriksson J, Taskinen MR. Different acute and chronic effects of acipimox treatment on glucose and lipid metabolism in patients with type 2 diabetes. Diabete Med 1993;10:950–7.
13. Worm D, Henriksen J, Vaag A, Thye-Rønn P, Melander A, Beck-Nielsen J. Pronounced blood glucose-lowering effect of the antilipolytic drug acipimox in non-insulin-dependent diabetes mellitus patients during a 3-day intensified treatment period. J Clin Endocrinol Metab 1994;78:717–21.
14. Collings P, Williams C, Macdonald I. Effects of cooking on serum glucose and insulin responses to starch. Br Med J 1981;282:1032.
15. Axelsen M, Arvidsson Lenner R, Lönnroth P, Smith U. Breakfast glycaemic response in patients with type 2 diabetes: effects of bedtime dietary carbohydrates. Eur J Clin Nutr 1999;53:706–10.
16. Chen Y, Cornblath M, Sidbury J. Cornstarch therapy in type 1 glycogen storage disease. N Engl J Med 1984;310:171–5.
17. Hayde M, Widhalm K. Effects of cornstarch treatment in very young children with type I glycogen storage disease. Eur J Pediatr 1990;149:630–3.
18. Wolfsdorf JI, Crigler JF Jr. Cornstarch regimens for nocturnal treatment of young adults with type I glycogen storage disease. Am J Clin Nutr 1997;65:1507–11.
19. Axelsen M, Wesslau C, Arvidsson Lenner R, Lönnroth P, Smith U. Bedtime uncooked cornstarch supplement prevents nocturnal hypoglycaemia in intensively treated IDDM subjects. J Intern Med 1999;245:229–36.
20. Axelsen M, Lönnroth P, Arvidsson Lenner R, Smith U. Suppression of the nocturnal free fatty acid levels by bedtime cornstarch in NIDDM. Eur J Clin Invest 1997;27:157–63.
21. DeFronzo R, Tobin J, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. Am J Physiol 1979;237:E214–23.
22. Forbes G, Gallup J, Hursh J. Estimation of total body fat from potassium-40 content. Science 1961;133:101–2.
23. Swedish Board of Agriculture. Food composition tables: energy and nutrients. Uppsala, Sweden: Liber Tryck AB, 1988.
24. Matthews J, Altman D, Campbell M, Royston P. Analysis of serial measurements in medical research. BMJ 1990;300:230–5.
25. Altman DG. Practical statistics for medical research. 2nd ed. London: Chapman & Hall, 1999.
26. Barter P, Nestel P. Precursors of plasma triglyceride fatty acids in obesity. Metabolism 1973;22:779–85.
27. Fulcher G, Farrer M, Thow H, et al. The glucose-fatty acid cycle in non-insulin dependent diabetes mellitus: the acute effects of inhibition of lipolysis overnight with acipimox. Diabetes Nutr Metab 1990;4:285–93.
28. Ratheiser K, Schneeweiss B, Waldhäusl W, et al. Inhibition by etomoxir of carnitine palmitoyltransferase I reduces hepatic glucose production and plasma lipids in non-insulin-dependent diabetes mellitus. Metabolism 1991;40:1185–90.


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29. Lewis G, Uffelman K, Szeto L, Weller B, Steiner G. Interaction between free fatty acids and insulin in the acute control of very low density lipoprotein production in humans. J Clin Invest 1995; 95:158–66.
30. Cummings M, Watts G, Umpleby A, et al. Acute hyperinsulinaemia decreases the hepatic secretion of very-low-density lipoprotein apolipoprotein B-100 in NIDDM. Diabetes 1995;44:1059–65.
31. Malmström R, Packard C, Caslake M, et al. Defective regulation of triglyceride metabolism by insulin in the liver in NIDDM. Diabetologia 1997;40:454–62.
32. Jeppesen J, Zhou M, Chen Y, Reaven G. Effect of metformin on postprandial lipemia in patients with fairly to poorly controlled NIDDM. Diabetes Care 1994;17:1093–9.
33. Chen Y-D, Swami S, Skowronski R, Coulston A, Reaven G. Effect of variations in dietary fat and carbohydrate intake on postprandial lipemia in patient with non-insulin-dependent diabetes mellitus. J Clin Endocrinol Metab 1993;76:347–51.
34. Chen Y-D, Coulston A, Zhou M-Y, Hollenbeck C, Reaven R. Why do low-fat high-carbohydrate diets accentuate postprandial lipemia in patients with NIDDM. Diabetes Care 1995;18:10–6.
35. Wolever TM, Jenkins DJ, Ocana AM, Rao VA, Collier GR. Second-meal effect: low-glycemic-index foods eaten at dinner improve subsequent breakfast glycemic response. Am J Clin Nutr 1988;48: 1041–7.
36. Björklund A, Yaney G, McGarry J, Weir G. Fatty acids and beta-cell function. Diabetologia 1997;40:B21–6.
37. Paolisso G, Tagliamonte M, Rizzo M, et al. Lowering fatty acids potentiates acute insulin response in first degree relatives of people with type II diabetes. Diabetologia 1998;41:1127–32.
38. Beck-Nielsen H, Groop L. Metabolic and genetic characterization of prediabetic states. Sequence of events leading to non-insulin dependent diabetes mellitus. J Clin Invest 1994;94:1714–21.
39. Boden G. Role of fatty acids in the pathogenesis of insulin resistance and NIDDM. Diabetes 1997;46:3–10.

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